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CLINICAL REVIEW

Distinctive patterns of cortical excitability to transcranial magnetic stimulation in obstructive sleep apnea syndrome, restless legs syndrome, insomnia, and sleep deprivation

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SUMMARY

Altered responses to transcranial magnetic stimulation (TMS) in obstructive sleep apnea syndrome (OSAS), restless legs syndrome (RLS), insomnia, and sleep-deprived healthy subjects have been reported. We have reviewed the relevant literature in order to identify eventual distinctive electrocortical profiles based on single and paired-pulse TMS, sensorimotor modulation, plasticity-related and repetitive TMS measures. Although obtained from heterogeneous studies, the detected changes might be the result of the different pathophysiological substrates underlying OSAS, RLS, insomnia and sleep deprivation rather than reflect the general effect of non-specific sleep loss and instability. OSAS tends to exhibit an increased motor cortex inhibition, which is reduced in RLS; intracortical excitability seems to be in favor of an "activating" profile in chronic insomnia and in sleep-deprived healthy individuals. Abnormal plasticity-related TMS phenomena have been demonstrated in OSAS and RLS. This review provides a perspective of TMS techniques by further understanding the role of neurotransmission pathways and plastic remodeling of neuronal networks involved in common sleep disorders. TMS might be considered a valuable tool in the assessment of sleep disorders, the evaluation of the effect of therapy and the design of non-pharmacological approaches.

Introduction

Transcranial magnetic stimulation (TMS), first introduced by Barker et al. in 1985 [1], is a painless and non-invasive neurophysiological technique specifically capable of assessing the primary motor cortex (M1) and the cortical–spinal tract excitability *in vivo*. In the last years, several TMS studies have been carried out to evaluate the neurophysiological pattern of cortical excitability in different sleep disorders, including obstructive sleep apnea syndrome (OSAS), restless legs syndrome (RLS), insomnia as well as experimentally sleep-deprived healthy subjects.

However, although the findings from these reports seem to reveal substantial changes of cortical excitability compared to healthy good sleepers, the complexity and heterogeneity of sleep disorders, the relatively low number of investigations and the heterogeneity in the methods employed preclude a comprehensive understanding. Studies assessing whether these changes might be distinctively related to the underlying pathophysiologic mechanisms of the different sleep disorders or they merely reflect the effect of disturbed nocturnal sleep are missing. It is well known, indeed, that sleep loss and instability are common features of OSAS [2,3], RLS [4,5] and insomnia [6,7].

When considering the wide spectrum of sleep loss disorders, it is useful to clarify the definition of different categories of sleep loss, such as total or partial sleep deprivation (SD), sleep fragmentation (SF) and insomnia. SD involves getting less than a sufficient amount of sleep and can include an acute total sleep-restricted state and a chronic partial sleep restriction state, as the complete absence of sleep over long periods is impossible for healthy humans. Total SD

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Abbreviations

CMCT	central motor conduction time
CSP	cortical silent period
EEG	electroencephalography
EMG	electromyography
GABA	gamma-aminobutyric acid
ICF	intracortical facilitation
ISI	interstimulus interval
LAI	long-latency afferent inhibition
LTD	long-term depression
LTP	long-term potentiation
M1	primary motor cortex
MEP	motor evoked potential
MRI	magnetic resonance imaging
MT	motor threshold
NMDA	N-methyl-D-aspartate
OSAS	obstructive sleep apnea syndrome
PAS	paired associative stimulation
REM	rapid eye movement
RLS	restless legs syndrome
rMT	resting motor threshold
rTMS	repetitive transcranial magnetic stimulation
SAI	short-latency afferent inhibition
SD	sleep deprivation
SF	sleep fragmentation
SICI	short-latency intracortical inhibition
TBS	theta burst stimulation
TMS	transcranial magnetic stimulation

Glossary of terms

Transcranial magnetic stimulation (TMS)
: non-invasive and painless neurophysiological technique specifically able to evaluate the excitability of motor cortical area and the cortical–spinal pathways conductivity through the administration of magnetic stimuli on the scalp.

Motor evoked potential (MEP)
: muscular response obtained after a single TMS pulse applied over the contralateral primary motor cortex at appropriate stimulation intensity.

MEP latency
: time interval between the administration of the TMS pulse on the motor cortex and the onset of the MEP from the contralateral target muscle; it reflects the conductivity of both the central and peripheral nervous systems, as well as neuromuscular junctions and muscles.

MEP amplitude
: it mainly reflects the excitation state of output cells in the motor cortex, nerve roots and the conduction along the peripheral motor pathway to the muscles.

Central motor conduction time (CMCT)
: latency difference between the MEPs induced by stimulation of the motor cortex and those evoked by spinal (motor root) stimulation; it reflects the integrity of the cortical–spinal tract, from the upper to the lower motor neurons.

Motor threshold (MT)
: lowest TMS intensity necessary to evoke MEPs in the target muscle when single-pulse stimuli are applied to the motor cortex, at rest (resting MT) or during contraction (active MT); it is a global measure of cortical excitability reflecting the excitability of cortical–spinal neurons and interneurons projecting onto these neurons in the motor cortex as well as of spinal motor neurons, neuromuscular junctions and muscle.

Cortical silent period (CSP)
: inhibitory MEP recorded during a sustained voluntary contraction of the target muscle followed by a suppression of the electromyographic activity evoked by a suprathreshold TMS stimulus applied to the contralateral motor cortex.

Paired-pulse transcranial magnetic stimulation
: TMS paradigm allowing to study intracortical inhibitory and excitatory phenomena by means of a conditioning subthreshold stimulus preceding a suprathreshold test stimulus by a programmable interstimulus interval.

Short-latency intracortical inhibition
: paired-pulse TMS measure obtained at short interstimulus interval in which the conditioning stimulus determines an inhibition with respect to the test stimulus; it is attributed to an activation of inhibitory neuronal system transmission.

Intracortical facilitation (ICF)
: paired-pulse TMS measure obtained at long interstimulus interval in which the conditioning stimulus determines an enhanced response with respect to the test stimulus; it is modulated by multiple neurotransmission pathways.

Short-latency afferent inhibition (SAI)
: inhibitory MEP resulting from an electric conditioning pulse applied on a peripheral nerve that precedes cortical TMS by a short interstimulus interval; it is considered as a putative marker of central cholinergic activity and allows to investigate the sensory-motor interaction within the cerebral cortex.

Long-latency afferent inhibition (LAI)
: as for SAI, but at longer interstimulus interval; in addition to the direct effects on MEP amplitude it also interacts with other cortical inhibitory circuits.

Paired associative stimulation (PAS)
: protocol consisting of slow-rate repetitive low-frequency nerve stimulation combined with TMS over the contralateral motor cortex; it has been shown to induce plastic changes of excitability in the human motor cortex.

Repetitive transcranial magnetic stimulation
: train of TMS pulses of the same intensity applied to a single brain area at a given frequency, that can transiently influence the function of stimulated and connected brain areas, mainly depending on the frequency of stimulation.

Theta burst stimulation (TBS)
: a form of high frequency repetitive TMS that, when applied to motor cortex, leads to after-effects on cortical–spinal and cortical–cortical excitability and that may reflect synaptic plasticity effects.

is typically defined as the length of time since the end of the last sleep period, whereas partial SD both by the length of the partial sleep period and the chronicity of the shortened sleep schedule. Conversely, SF refers to the interruption of a sleep stage as a result of the appearance of a lighter stage or of the occurrence of wakefulness, which leads to disrupted non-rapid eye movement (REM)/REM sleep cycles [8]. The occurrence of brief arousals throughout the night also reduce the total amount of sleep time and is associated to a loss of hippocampal long-term potentiation and related cognitive consequences [9]. Finally, according to the 2nd edition of the International Classification of Sleep Disorders (ICSD-2) [10] and specific research criteria [11], insomnia is defined as the difficulty in initiating and/or maintaining sleep, that includes extended periods of nocturnal wakefulness and/or insufficient amounts of nocturnal sleep that occurs despite adequate time and opportunity for sleep. This apparent chronic reduction in total sleep should leave these patients suffering from chronic partial SD. However, patients with chronic insomnia are not more sensitive to SD than normal sleepers and do not have sleep rebounds, as normal sleepers would, after their typically poor sleep [8]. It seems most likely that many patients with primary insomnia have relatively small reductions in their total sleep time and that any residual sleepiness associated with this reduction is masked by the arousal system. Patients with insomnia, indeed, do not typically display significant daytime sleepiness probably because the insomnia state is usually accompanied by a sleep loss which is less than subjectively reported, rather than a chronic partial SD [8].

Taking into account these considerations, the goal of this paper is to critically and systematically review the literature in order to determine if the brain structure excitability abnormalities to TMS, in patients with OSAS, RLS and insomnia as well as in experimentally-deprived healthy subjects, represent specific neurophysiological markers of the different sleep disorders, possibly correlated and useful for the identification of disease-specific mechanisms, or if they are a general consequence of the sleep architecture alteration.

Therefore, different scenarios can be hypothesized: 1) identification of specific patterns of cortical excitability linked to a distinctive sleep disorder; 2) identification of non-specific patterns of cortical excitability, associated to the general mechanisms of disturbed sleep and common to all sleep disorders considered here; 3) identification of patterns of cortical excitability characterized by some disease-specific markers admixed with less specific features dependent on the mechanisms of sleep loss and instability. The eventual identification of distinctive profiles of cortical excitability in OSAS, RLS, insomnia and experimentally-induced SD would help to depict neurophysiological changes consistent with the involvement of different neurobiological substrates for these conditions and confirm the conclusions reached in the literature; otherwise, a reconsideration of the meaning of these changes would be needed.

Methods and materials

Data source and selection

To identify all studies available on TMS and OSAS, RLS, insomnia and SD, a PubMed-based literature review of TMS studies on these sleep disorders was conducted. The keywords used in this search were: “transcranial magnetic stimulation”, “sleep”, “apnea”, “restless legs syndrome”, “insomnia”, “sleep deprivation”.

The following data were extracted: 1) study design; 2) patients characteristics, such as number of patients enrolled, age, gender, laterality, presence/absence of treatment, time of the day, wakefulness/sleep state; 3) TMS methods and stimulator/coil features; 4) results of TMS parameters as indicated in the section below.

Transcranial magnetic stimulation parameters

A variety of TMS motor cortex excitability measures can be obtained, each related to distinct neurobiological and neurochemical processes. We have reviewed here studies evaluating single-pulse, paired-pulse and plasticity-related TMS variables.

Single-pulse TMS variables

A single TMS pulse applied over M1 elicits a motor evoked potential (MEP) in the contralateral target muscles [12] and may provide a functional assessment of the cortical–spinal conduction. In particular, the latency of MEP and the central motor conduction time (CMCT), defined as the latency difference between the MEPs induced by motor cortex stimulation and those evoked by motor root stimulation, are measures of the integrity of the cortical–spinal pathways, while the amplitude of the MEP is an aggregate measure of the excitation state of output cells in the motor cortex. Resting motor threshold (rMT) is defined as the minimum stimulus intensity which is required to produce a MEP amplitude >50 μV in at least five of 10 consecutive trials at rest and it is believed to provide information about a central core of neurons in the muscle representation of the primary motor cortex [13]. Resting motor threshold (MT) is increased by drugs that block voltage-gated sodium channels [14], is not affected by drugs with effects on gamma-aminobutyric acid (GABA) [15], and is lowered by drugs increasing glutamatergic transmission not mediated by N-methyl-D-aspartate (NMDA) [16], suggesting that rMT reflects both neuronal membrane excitability and non-NMDA receptor glutamatergic neurotransmission. Motor threshold is typically increased if a significant portion of the cortical–spinal tract is damaged, while it decreases in situations of a hyperexcitable cortical–spinal system. When the single magnetic pulse is delivered during a voluntary contraction of the contralateral target muscle, the MEP is followed by a suppression of the electromyographic (EMG) activity. This phenomenon, called cortical silent period (CSP), is indeed a measure of the suppression of the cortical–spinal output at a cortical level, probably due to the activation, after an early spinal phase (its first 50–75 ms), of inhibitory cortical interneurons mainly mediated by GABA-B transmission [17,18].

Paired-pulse TMS variables

TMS also may be used to investigate the intracortical inhibitory and facilitatory mechanisms within the motor cortex. Some of these TMS techniques involve paired stimulation, in which a conditioning subthreshold stimulus precedes a suprathreshold test stimulus by a programmable interstimulus interval (ISI). Paired-stimuli TMS has revealed the existence of a complex of inhibitory and excitatory intracortical interactions within the human brain [19,20], mainly depending on the ISI employed. At short ISI (1–5 ms), the conditioning stimulus determines a short-latency intracortical inhibition (SICI) with respect to the test stimulus, whereas at longer ISI (7–20 ms), the effect is an intracortical facilitation (ICF). SICI and ICF are considered to arise from different neural circuits: SICI is thought to reflect mostly the excitability of inhibitory GABAergic cortical circuits [21–23]; ICF is considered to depend on the activity of intracortical glutamatergic excitatory circuits [24,25], since dextromethorphan, an NMDA receptor antagonist, reduces the ICF [26]. However, the neurochemical network underlying ICF seems to be more complex because it involves various neurotransmission pathways, supporting the hypothesis that ICF is a complex cortical–subcortical neurophysiological phenomenon [19].

Table 1
Transcranial magnetic stimulation studies in obstructive sleep apnea syndrome (OSAS).

Study	Civardi C et al. 2004 [40]		Grippo A et al. 2005 [41]		Sériès F et al. 2009 [42]	
	Patients	Controls	Patients	Controls	Patients	Controls
Participants	7 (4 M)	9 (5 M)	10 (9 M)	10 (8 M)	13 M	8 M
Age ± SD (range) (y)	32.7 ± 12.7	36.4 ± 10.3	56 (31–67)	47 (31–61)	49 ± 6 (40–59)	49 ± 5 (40–56)
Coil/muscles/hemisphere	Circular/FDI/right		Circular/FDI/dominant		Circular/GG/DI/APB/dominant	
Time/condition	Wake (150% of the rMT)/sleep		Wake every two hours (10:00 h – 18:00 h))		Various stages of breathing/protrusion of the tongue	
Treatment	None		None		None	
MEP latency	NS, increased (hand muscle only during sleep)		NS		Decreased in DI and GG during tongue protrusion in OSAS	
MEP size	NS, decreased (hand muscle only during sleep)		NS (ratio)		Increased in GG during inspiration and in ABP during tongue protrusion in OSAS	
CMCT	NR		NS		NR	
MT	NS		NS		Increased difference between GG and DI during respiration in OSAS	
CSP	Increased		Increased		NP	
ICI	NP		NP		NP	
ICF	NP		NP		NP	
Notes			Correlation with $PaCO_2$		Correlation between GG latencies and AHI	

Study	Wang W et al. 2010 [43]		Joo EY et al. 2010 [44]		Opie GM et al. 2013 [45]	
	Patients	Controls	Patients	Controls	Patients	Controls
Participants	12 M	12 M	45 M	44	13 (11 M)	11 (9 M)
Age ± SD (range) (y)	49 ± 4	51 ± 6	47.2 ± 9.7	47.2 ± 5.4	42.6 ± 10.2	43.0 ± 10.3
Coil/muscles/hemisphere	Figure-of-eight/GG/dominant		Figure-of-eight/FDI/dominant		Figure-of-eight/FDI, ADM/dominant	
Time/condition	Wakefulness, at the end of expiration and inspiration		At rest		Wakefulness	
Treatment	None		None		None	
MEP latency	Decreased		NP		NP	
MEP size	NS		NR		NR	
CMCT	Decreased		NP		NR	
MT	NP		Increased		Increased at rest, NS for active	
CSP	NP		Increased		NP	
ICI	NP		NS (ISI 2–3–5)		NS	
ICF	NP		NS (ISI 10–15–20)		NP	
Notes	Correlation with AHI, saturation, apnea time		No correlation		Lack of response to continuous TBS	

Study	Das A et al. 2013 [46]		Melo-Silva CA et al. 2013 [47]		Melo-Silva CA et al. 2013 [48]	
	Patients	Controls	Patients	Controls	Patients	Controls
Participants	13 (10 M)	12 (8 M)	14 (11 M)	0	10 (9 M)	0
Age ± SD (range) (y)	47.7 ± 9.7	46.2 ± 10.5	50 ± 14	/	51 ± 13	/
Coil/muscles/hemisphere	Figure-of-eight/FDI/dominant		Figure-of-eight/submental/non-dominant		Figure-of-eight/submental/non-dominant	
Time/condition	Wakefulness		Wakefulness and sleep		Wakefulness and sleep	
Treatment	None		CPAP in 7, zolpidem		Zolpidem	
MEP latency	NS		NS wakefulness vs. sleep		NS wakefulness vs. sleep	
MEP size	NS		NS wakefulness vs. sleep		NS wakefulness vs. sleep	
CMCT	NS		NP		NP	
MT	Increased at rest		Increased in submental muscle during sleep		Increased in submental muscle during sleep	
CSP	Increased		NP		NP	
ICI	NP		NP		NP	
ICF	NP		NP		NP	
Notes	Lack of response to high-frequency rTMS over M1 in patients (not in controls)		Cortico-bulbar excitability of submental muscles decreased during NREM sleep		TMS-induced twitches reduced flow limitation during sleep in OSAS	

ABP: abductor pollicis brevis muscle; ADM: abductor digit minimi muscle; AHI: apnea-hypopnea index; CMCT: central motor conduction time; CPAP: continuous positive airway pressure; CSP: cortical silent period; DI: diaphragmatic muscle; FDI: first dorsal interosseus muscle; GG: genioglossus muscle; ICF: intracortical facilitation; ICI: intracortical inhibition; ISI: interstimulus interval; M: male; M1: primary motor cortex; MEP: motor evoked potentials; MT: motor threshold; NP: not performed; NR: not reported; NS: not significant; OSAS: obstructive sleep apnea syndrome; rMT: resting motor threshold; rTMS: repetitive transcranial magnetic stimulation; SD: standard deviation; TBS: theta burst stimulation.

TMS measures of sensory-motor modulation

Using a different TMS paradigm, it is possible to investigate the sensory-motor interaction within the cerebral cortex and the cortical phenomenon of the short-latency afferent inhibition (SAI) and long-latency afferent inhibition (LAI). SAI refers to the suppression of the amplitude of the MEP produced by a conditioning afferent electrical stimulus applied to the median nerve at wrist approximately 20 ms prior to TMS of the hand area of the contralateral motor cortex [27]. SAI is thought to reflect the integrity of central cholinergic neural circuits, as it has been shown to be reduced or abolished by the muscarinic antagonist scopolamine in healthy subjects [28] and is positively modulated by acetylcholine [29]. On the other hand, it has been suggested that SAI may depend on the integrity of circuits linking sensory input and motor output [30], and other neurotransmitters (dopamine, in particular) are supposed to play a modulatory role on the cholinergic

transmission. LAI is probably related to the cortical–cortical connections involving the motor cortex and both primary and secondary somatosensory cortical areas.

Plasticity-related TMS measure and repetitive TMS

Transcranial magnetic stimulation allows to study the synaptic plasticity phenomena at different levels. In healthy subjects, TMS applied after a brief period of exercise reveals the "post-exercise facilitation" and the "delayed facilitation" phenomena, providing valuable information on cortical excitability and intracortical synaptic reorganization underlying motor learning [31]. Single TMS pulses delivered in trains are the principle of repetitive TMS (rTMS), an approach that can transiently influence the function of stimulated and connected brain areas [32,33], mainly depending on the frequency of stimulation. Repetitive TMS might have therapeutic and rehabilitative applications since the effects of repeated sessions may persist in time, inducing long-lasting neuroplastic changes. Generally low-frequency rTMS (stimulus rates of <1 Hz) induces inhibitory effects on motor cortical excitability, allowing creation of a reversible virtual lesion [34], while high-frequency rTMS (5–20 Hz) usually promotes an increase in cortical excitability [35,36]. This modulation can last for several minutes, depending on the duration of the train itself, and also provides an index of plasticity. The mechanisms of these changes are not clear, but seem to be related to synaptic long-term potentiation (LTP) and long-term depression (LTD) in the central nervous system [37,38]. Similarly it is possible to induce LTP-like changes in the sensory-motor system at the level of M1, by means of an experimental intervention known as paired associative stimulation (PAS). PAS involves a stimulus to a peripheral nerve (usually the median nerve) followed by a single TMS pulse applied over the hand area of the motor cortex [39]. PAS induces a lasting increase in cortical–spinal excitability, which can be considered to be a marker of motor cortical plasticity, with long-term plasticity-like mechanisms thought to play a major role [39].

Results

With an initial search using the keywords "transcranial magnetic stimulation" and "sleep", 202 articles were screened in total. Adding another keyword ("apnea"), we sorted out 21 articles. Using the keywords "transcranial magnetic stimulation" and "restless legs syndrome" we found 20 articles. Finally, using the keywords "transcranial magnetic stimulation" and "insomnia" and "sleep deprivation" we sorted out 13 and 47 articles, respectively.

We excluded articles about TMS and sleep in depressed patients, studies conducted in animals and also TMS studies on narcolepsy because their content did not fit the aim of this review. Moreover, we did not include all non-conclusive studies as well as preliminary or low-quality data in order to avoid to draw misleading results and conclusions. We also excluded articles different from research studies (such as reviews, letters to the Editor, etc…) as well as non-English written papers. We have reviewed the articles listed in references of the papers retrieved to locate further data on TMS and sleep disorders.

After this process, we identified nine TMS studies in OSAS patients [40–48], 14 in RLS patients [49–62], one in individuals suffering from insomnia [63] and eight in sleep-deprived healthy subjects [64–71].

Tables 1–3 provide the sample characteristics, the methodological approach and a summary of the findings on all the TMS studies reviewed here investigating motor cortical excitability in OSAS, RLS and sleep-deprived subjects.

Single-pulse TMS variables

Motor evoked potentials

Of the nine TMS studies in OSAS patients, only six investigated the changes in the cortical–spinal pathway. Two studies exploring the cortical–spinal excitability in hand muscles demonstrated that it was unaffected during wakefulness [40,41], although one of them indicated a depression of the cortical-motoneuronal excitability during apnea [40]. Only one study investigated phrenic nerve conduction, recording MEPs from the diaphragm muscle [72]. The authors showed a possible involvement of the cortical-diaphragmatic pathway because of the absence of response or a reduction in MEP amplitude, although these findings need replication. Two other studies explored TMS responses from the genioglossus and the diaphragm muscles to facilitatory maneuvers. One showed that this pattern differs from the controls in favor of a more evident facilitation in OSAS patients [42], whereas the other report showed an increased central motor conductivity of the genioglossus in OSAS patients, related to the severity of the disease. The authors argued that this finding could be the effect of a facilitation or of a central compensatory mechanism [43]. MEPs in subjects with OSAS were not found to be significantly different from those of healthy controls in a recent study in awake OSAS patients [46].

In patients with RLS, the cortical–spinal pathway seems to be unaffected [51,52,54,55,58,59] whereas no study evaluated the cortical–spinal integrity in patients with insomnia. After SD, healthy subjects did not show significant changes of the MEPs amplitude [64,65,68,71].

Resting MT

We have identified eight published reports evaluating motor cortex excitability in patients with OSAS. Two studies did not find a difference in rMT values between patients and healthy subjects in the awake state [40,41]. However, in the study by Civardi et al. [40] a reduction of MEP size and a prolongation of MEP latency were described during non-REM sleep stage 2 and these abnormalities appeared to be more pronounced during apneas. The other three studies, using a figure-of-eight TMS coil, showed decreased motor cortex excitability in hand muscles as indexed by the increase of rMT [44–46]. A further study assessing cortical-motor control in awake OSAS patients showed increased MEP amplitude and decreased MEP motor threshold from genioglossus during inspiratory TMS in OSAS [42]. Finally, two recent papers evaluating the efficacy of consecutive TMS twitches in reducing flow-limitation during sleep in OSAS patients, observed an increase of rMT from the submental muscle during sleep [47,48], suggesting that cortical-bulbar excitability of submental muscles decreases during NREM sleep.

Most of papers exploring rMT in RLS converge on the finding that motor cortex threshold is not impaired in these patients [49,50,52,54–60], with the exception of the studies by Stiasny-Kolster et al. [51], who reported a trend for increased active MT in the tibialis anterior muscle, and by Gunduz et al. [62], who observed a decreased active MT from first dorsal interosseous muscle only during nighttime.

Only one study was performed in patients with insomnia. Resting MT was similar to that of controls, although a greater recruitment of the MEPs was evident in patients [63]. SD seems to increase the risk for epileptic seizures in both healthy individuals and patients with epilepsy. After SD there was no significant change of rMT [44,64,66–68,70,71], although the cortical recovery curve showed an increase in cortical excitability at the 250-ms ISI [67]. However, contrasting results emerged from recent research using combined electroencephalography (EEG) and TMS protocols. Prolonged wakefulness and artificial SD seem to be characterized by a global increase in cortical excitability over the frontal areas that is

Table 2
Transcranial magnetic stimulation studies in restless legs syndrome (RLS).

Study	Tergau F et al. 1999 [49]		Entezari-Taher M et al. 1999 [50]		Stiasny-Kolster K et al. 2003 [51]		Quatrale R et al. 2003 [52]	
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls
Participants	18 (13 F)	17 (12 F)	10	10	15 (10 F)	15 (10 F)	15	10
Age ± SD (range) (y)	63.1 ± 10.8 (44–77)	59.7 ± 12.8 (39–82)	52 ± 9	49 ± 12	55.4 ± 9.3 (38–72)	55.4 ± 9.6 (38–71)	60.5 ± 25.4	59.1 ± 19.1
Coil/muscles/hemisphere	Figure-of-eight/ADM, AH/left hemisphere		Circular/APB/TA		Circular/ADM/TA/right hemisphere		Figure-of-eight (arms)/ circular (legs)/ADM, TA, EDB/right handed, bilateral	
Time/condition	Late afternoon				8:00 h – 20:00 h		9:00 h	
Treatment	>24 h off medication		>48 h off medication		Pre- and post-treatment with L-dopa		None	
MEP latency	NR		NR		NR		NS	
MEP size	NR		NR		NR		NS	
CMCT	NR		NR		NS		NS	
MT	NS (both active and resting)		NS		Active increased in TA, trend in ADM		NS	
CSP	NS		Decreased, at 150% of the rMT		Decreased TA L-dopa restored CSP		NS	
ICI	Decreased in both (especially in patients with afternoon symptoms)		NP		NP		Decreased in ADM and TA (especially in the affected side)	
ICF	Increased in ADM, decreased in AH (especially in patients with afternoon symptoms)		NP		NP		Increased in ADM and in TA (especially in the affected side)	
SAI	NP		NP		NP		NP	
LAI	NP		NP		NP		NP	
Post-exercise MEP facilitation	NP		NP		NP		NP	
PAS	NP		NP		NP		NP	

Study	Scalise A et al. 2004 [53]		Scalise A et al. 2006 [54]		Nardone R et al. 2006 [55]		Kutukcu Y et al. 2006 [56]		Gorsler A, Liepert J 2007 [57]	
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls
Participants	6	2	11 (6 F)	11 (6 F)	14 (6 F)	15 (6 F)	20 (16 F)	15 (9 F)	10	7
Age ± SD (range) (y)	NR	NR	59.6 ± 4.1	49.4 ± 3.1	58.5 ± 8.8	56.2 ± 6.0	53.6 (39–70)	53.5 (27–74)	(45–67)	(38–64)
Coil/muscles/hemisphere	Circular/FDI/right handed, right hemisphere		Circular/FDI/right handed, right hemisphere		Figure-of-eight/FDI/ dominant		Circular/ABP, TA/right handed, bilateral		Circular/TA/left	
Time/condition	Late morning Post-exercise		Late morning		8:00 h 20:00 h		NR		8:00 h 20:00 h	
Treatment	None		None		Pre- and post-dopaminergic (one month)		Pre- and post-dopaminergic (one month)		Pre- and post-dopaminergic (two weeks, three months)	
MEP latency	NR		NR		NR		NR		NR	
MEP size	NR		NS		NR		NR		NR	
CMCT	NR		NR		NS		NR		NR	
MT	NR		NS		NS both active and at rest		NS		NS	
CSP	NR		Decreased		NS		Decreased in TA treatment restored CSP		Decreased treatment restored CSP	
ICI	Decreased (ISI 1–6)		Decreased (ISI 1–6)		Decreased (ISI 1,3,5) treatment restored ICI		NP		NP	
ICF	NR		NP		NS (ISI 7, 10, 20)		NP		NP	
SAI	NP		NP		NP		NP		NP	
LAI	NP		NP		NP		NP		NP	
Post-exercise MEP facilitation	Decreased absence of delayed facilitation		Decreased		NP		NP		NP	
PAS	NP		NP		NP		NP		NP	

Study	Rizzo V et al. 2009 [58]		Scalise A et al. 2010 [59]		Rizzo V et al. 2010 [60]		Ahlgrén-Rimpiläinen A et al. 2012 [61]		Gunduz A et al. 2012 [62]	
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls
Participants	12 (6 F)	10 (4 F)	12 (8 F)	12	10 (6 F)	10 (5 F)	6 (3 F)	6 (3 F)	11 (5 F)	8 (4 F)
Age ± SD (range) (y)	53.4 ± 12.5	51.8 ± 5.6	52.7 ± 10.9	49.4 ± 3.1	50 ± 13	52 ± 6	60.3 ± 10.3	41.2 ± 5.9	50.2 ± 13.3	48.1 ± 16.9
Coil/muscles/hemisphere	Figure-of-eight/APB/right handed, left hemisphere		Circular/FDI/right handed, non-dominant		Figure-of-eight/ right APB/right handed		Circular/ADM, TA/right handed, bilateral		Circular/FDI/NR	
Time/condition	15:00 h		Late morning		15:00 h		Daytime		Afternoon and 22:00 h – 23:00 h	
Treatment	Pre- and post-dopaminergic (1 mo)		Pre- and post-dopaminergic (1 mo)		Pre- and post-dopaminergic		None or pharmacological wash out		None	

Table 2 (*continued*)

Study	Rizzo V et al. 2009 [58]		Scalise A et al. 2010 [59]		Rizzo V et al. 2010 [60]		Ahlgrén-Rimpiläinen A et al. 2012 [61]		Gunduz A et al. 2012 [62]	
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls
MEP latency	NR		NR		NR		NS		NS	
MEP size	NS		NS		NR		NR		NS	
CMCT	NR		NR		NR		NS		NS	
MT	NS		NS		NS, active and at rest		NP (stimulation intensity constantly above MT)		Decreased active during nighttime	
CSP	NP		Decreased		NP		Duration NS (multiple CSP in both ADM and in the dominant TA)		NS	
ICI	NP		Decreased, treatment restored ICI (ISI 3 ms)		Decreased (ISI 2 ms) treatment restored ICI		NP		NP	
ICF	NP		NP		NS (ISI 12 ms)		NP		NP	
SAI	NP		NP		Decreased, dopaminergic treatment restored SAI		NP		NP	
LAI	NP		NP		NS		NP		NP	
Post-exercise MEP facilitation	NP		Decreased increased after treatment		NP		NP		NP	
PAS	NS PAS associative plasticity restored by treatment		NP		NP		NP		NP	

ABP: abductor pollicis brevis muscle; ADM: adductor digit minimi muscle; AH: abductor hallucis muscle; CMCT: central motor conduction time; CSP: cortical silent period; EDB: extensor digitorum brevis muscle; F: female; FDI: first dorsal interosseus muscle; ICF: intracortical facilitation; ICI: intracortical inhibition; ISI: interstimulus interval; LAI: long-latency afferent inhibition; MEP: motor evoked potentials; MT: motor threshold; NP: not performed; NR: not reported; NS: not significant; PAS: paired associative stimulation; SAI: short-latency afferent inhibition; SD: standard deviation; TA: tibialis anterior muscle.

reverted back to normal during sleep [73]. This result had already been reported in deprived patients with juvenile myoclonic epilepsy [67,68,74]. On the contrary, after 40 h of SD in healthy individuals, rMT seems to increase, together with theta rhythms, in the left frontal and prefrontal cortex [69].

Cortical silent period

All studies investigating CSP in patients with OSAS reported a significant prolongation of the CSP [40,41,44,46]. On the contrary, many studies in patients with RLS showed that CSP is markedly reduced [50,51,54,57,59] and this result seems to be stable across the day [51]. Interestingly, several investigations [51,55–60] evaluated the effect of acute or chronic treatment with L-dopa or dopamine-agonist drugs, such as cabergoline or pramipexole, on these measures. In particular, some of them agreed in showing that the shortening of CSP is reversed by drugs acting on the dopaminergic system [51,56,57]. However, other investigators did not observe significant changes of CSP duration between RLS patients and controls [49,52,55,61,62].

The only study in patients with chronic insomnia did not include CSP among the parameters investigated [63]. Some studies have reported that CSP was unaffected after SD in healthy subjects [64], although in another study CSP duration was reported to be decreased [66,68,70]. Moreover, a recent investigation found a significant reduction in the duration of CSP in ten normal subjects who underwent selective REM SD [71].

Paired-pulse TMS variables

Short-latency intracortical inhibition

Of the nine studies on OSAS included in this review, only two studied SICI [44,45], which was found not to be significantly different compared to controls, although these few data do not allow to draw stable conclusions. On the contrary, ICI is markedly reduced in RLS [49,52–55,59,60], especially in the most severely affected side [52] and in patients with afternoon symptoms [49]. Similarly to the effects of dopaminergic drugs on CSP, treatment with cabergoline and pramipexole seems to revert back to normal the changes at the level of the intracortical inhibitory circuits [55,59,59,60]. SICI was found to be scant in patients with insomnia [63] whereas, some studies in sleep-deprived healthy subjects showed a relative flattening of the paired-pulse curve, with a reduction of both inhibition [54,64,66,70], and facilitation [64], suggesting that this condition might be associated with a general hypoexcitability of the cortical interneurons. Nevertheless, other investigators did not observe a significant difference in the ICI [65,68,69] functioning before and after SD, and one study only reported increased inhibition during the night, with a return to baseline values in the morning [65]. Finally a recent study on selective REM SD described a significant reduction of ICI, thus adding support to the probable proconvulsant role of REM sleep loss [71].

Intracortical facilitation

The only study exploring ICF in OSAS showed that it seems to be preserved in this group of patients [44]. Two studies on patients with RLS seem to indicate that the ICF is preserved [55,60], although other two found a hyperfacilitation in RLS [49,52] especially in the affected side [52] and in patients with afternoon symptoms [49].

ICF was reduced in the only existing study on patients with insomnia [63]. On the contrary a study showed a significant increase of ICF after 40 h of SD but only in females [69], suggesting some caution in the generalization of these results. However, the majority of the studies exploring facilitatory intracortical phenomena found ICF to be unchanged [65,68,70,71].

Sensory-motor modulation TMS measures

Only one study investigated the sensorimotor integration in patients with RLS whereas it has never been investigated in patients with OSAS or insomnia. The authors found that SAI, but not LAI, was significantly reduced in RLS and that this change was restored after a month of dopaminergic treatment [60].

Table 3
Transcranial magnetic stimulation studies in sleep-deprived healthy subjects.

Study	Civardi C et al. 2001 [64]	Manganotti P et al. 2001 [65]	Scalise A et al. 2006 [66]	Badawy RA et al. 2006 [67]
Participants	8 (4 M)	7 (3 M)	7 (4 M)	13 (7 M)
Age ± standard deviation (range) (y)	28.7 ± 4.2 (25–37)	(24–35)	(26–38)	39.2 (21–73)
Coil/muscles/hemisphere	Figure-of-eight/FDI/left	Circular/thenar eminence muscles/left	Figure-of-eight/APB/right	Circular/APB/dominant
Time/condition	Before and after 24 h of SD	Recordings every 6 h during day-time and every 3 h during night-time	Late morning/before and after 24 h of SD	Before and after 20 h of SD
MEP latency	NR	NR	NR	NR
MEP size	NS	NS	NR	NR
MT	NS	Decreased during the late recordings in the night; baseline values in the morning	NS	NS
Recovery curve	NP	NP	NP	Increased at ISI 250 ms
CSP	NS	Increased only at intensity of 130% of the rMT	Decreased	NP
ICI	Decreased (ISI 2–3 ms)	Increased during the night, with a return to baseline values in the morning (ISI 1–4)	Decreased (ISI 1–6 ms)	NP
ICF	Decreased (ISI 14–16 ms)	NS (ISI 10–15)	NP	NP

Study	Manganotti P et al. 2006 [68]	De Gennaro L et al. 2007 [69]	Kreuzer P et al. 2011 [70]	Placidi F et al. 2013 [71]
Participants	10 (5 M)	33 (18 M)	15 (11 M)	10 (4 M)
Age ± standard deviation (range) (y)	(18–30)	24.6 ± 2.4	24.3 ± 2.7 (21–30)	25.4 ± 3.1 (20–30)
Coil/muscles/hemisphere	Circular/APB/left	Figure-of-eight/ ADM/left	NR/ADM/left	Figure-of-eight/opponens pollicis/non-dominant
Time/condition	Early morning/before and after 9–10 h of SD	Before and after 40 h of SD	8:00h/after normal night sleep and total SD of at least 24 h	Late morning/after a full night of spontaneous sleep, after a night of SRD and after a night with non-REM sleep awakenings
MEP latency	NR	NP	NP	NP
MEP size	NS	NP	NR	NS
MT	NS	Increased	NS	NS
Recovery curve	NP	NP	NP	NP
CSP	NS	NP	NS	Decreased after SRD
ICI	NS (ISI 1–4 ms)	NS	Decreased	Decreased after SRD (ISI 2 ms)
ICF	NS (ISI 10–15 ms)	Increased in females	NS	NS

ABP: abductor pollicis brevis muscle; ADM: abductor digit minimi muscle; CSP: cortical silent period; ICF: intracortical facilitation; ICI: intracortical inhibition; ISI : inter-stimulus interval; FDI: first dorsal interosseus muscle; MT: motor threshold; NP: not performed; NR: not reported; NS: not significant; SD: sleep deprivation; M: male; MEP: motor evoked potentials; rMT: resting motor threshold; SRD: selective REM sleep deprivation.

Plasticity-related TMS measures and repetitive TMS

Overall, there are few studies on cortical plasticity and sleep disorders in the literature. Three reports showed a decrease of post-exercise facilitation in response to TMS in RLS patients [53,54,59] and one of them also found that the administration of dopamine agonists was able to reverse the delayed facilitation [59].

Moreover, a TMS study showed that the PAS protocol did not change MEPs amplitude in patients with idiopathic RLS without treatment and that the associative plasticity was restored after four weeks of dopaminergic treatment [58].

Recently, plasticity was investigated in OSAS using the rTMS and theta burst stimulation (TBS) protocol. These studies showed that MEPs characteristics did not change in patients with OSAS after the application of high-frequency rTMS [46] or continuous TBS [45].

The use of rTMS in sleep disorders might also have therapeutic applications, since the effect of repeated sessions may persist over time [37]. In this context, the efficacy of rTMS in the treatment of patients with chronic primary insomnia has been recently assessed in terms of improvement of stage III sleep and REM sleep cycle [75]. Similarly, high-frequency rTMS guided with functional magnetic resonance imaging (MRI) and applied to the left lateral occipital cortex while SD healthy subjects performed a working memory task did not exhibit degraded performance typical in SD but a performance similar to healthy good sleepers [76].

Discussion

Regarding the main scope of this review, i.e., to identify eventual disease-specific TMS parameter changes, despite the many methodological differences of the various studies (patient selection and features, type of TMS coil, muscles explored, time of the day, awake state, hemisphere), the data here reviewed seem to converge on the idea that the changes detected might be probably the expression of the different and still largely unknown pathophysiological substrates of OSAS, RLS and insomnia rather than a more general impact of a common mechanism connected with sleep loss and instability on the motor cortex excitability. Some differences seem to emerge from the investigations included in this analysis when considering the different conditions from a pure neurophysiological point of view. However, these differences must be viewed in light of some important limitations, such as the relatively small patient samples enrolled and the fact that the majority of these studies did not take into account sleep quality and sleep EEG data. Different sleep EEG parameter modifications induced by RLS and OSAS may indeed cause the excitability changes detected by TMS. In a quantitative EEG study of Morrison et al. [77], EEG slowing in REM sleep was observed over frontal, central and parietal regions in apneic patients, while EEG slowing during wakefulness was observed over all cortical regions examined. Moreover, a positive

correlation was found between EEG slowing during wakefulness and oxygen desaturation during the night [77] The same researchers observed that in apneic patients, compared to normal controls, abnormal EEG slowing was present in frontal and central regions during both wakefulness and REM sleep and that treatment with continuous positive air pressure was found to correct the EEG slowing for both REM sleep and wakefulness [78]. This EEG slowing in the frontal–central regions in OSAS patients may influence TMS results and be correlated with a global pattern of reduced excitability of the motor cortex.

In RLS subjects, EEG spectral analysis of waking-rest conditions has revealed an increased high beta band power, primarily in the anterior scalp regions [79]. High frequency activity in the beta band is thought to reflect cortical activation that represents an analog of sensory processing, attention focusing, or working memory [80–82]. These EEG findings seem to indicate the presence of a cortical dysfunction in RLS patients, in terms of a hyperarousal state, that might support the detection of impaired inhibitory pathways at the level of TMS. However, it has also been reported that TMS abnormalities show a circadian distribution pattern [62] and that they can be reversed by dopamine agonist treatment [51,55–60]. These studies have focused their attention on intracortical inhibitory/excitatory mechanisms but the arousal system has a more complex pathophysiology involving several subcortical structures [83]; additionally, an abnormal spinal excitability is believed to underline most of the RLS symptomatology [84,85]. In this context, it is not trivial that an increased motor spinal cord excitability was believed to be at the basis of subclinical but significant changes in daytime muscle activation patterns during gait in RLS patients [86].

Finally, we are currently unable to support the potential role of SF in the sleep disorders considered here regarding changes of cortical excitability detected by TMS. The lack of previous studies, indeed, does not allow to assess whether the SF can affect cortical inhibition as SD does. However, a preliminary investigation has been carried out aiming at evaluating the effect of SF on TMS cortical excitability in healthy subjects and the presence of post-exercise facilitation and delayed facilitation [87]. The results indicate that SF might produce significant disruption of nocturnal sleep, reduce daytime alertness, and increase sleepiness, along with a significant increase of the rMT; on the other side, SF was unable to modify both cortical inhibition and cortical plasticity. These findings seem to be in contrast to TMS changes observed in SD and RLS. The authors argued that a possible explanation of these apparent contradictions is that SD and SF probably represent different phenomena that can depend on various networks acting on motor cortex. SF seems to impair the restorative cognitive benefits of sleep via alterations in hippocampal synaptic plasticity, involving mechanisms different from SD [87].

Nevertheless, taking into account these considerations, some distinctive differences at the level of TMS may be identified between the sleep disorders considered here. First of all, some TMS findings have suggested the possible existence of a widespread alteration of conductivity in hand muscles only during sleep [40]. This cortical–spinal, rather than pure intracortical, mechanism does not occur neither in patients with RLS [51,52,54,55,58,59,61,62] nor in patients with chronic insomnia [63]. As suggested by Civardi et al. [40], a further drop in the cortical-motoneuronal excitability is strictly associated with apneas in this group of OSAS patients, although whether this phenomenon is related to hypoxia/hypercapnia or to fatigue remains to be clarified. A cortical-diaphragmatic involvement has been reported in OSAS [72], although this finding has not been replicated, thus limiting the interpretation.

However, the most relevant data are related to the distinctive changes of measures of motor cortex excitability, adding support to the hypothesis that the cortical excitability abnormalities reported while awake in these studies might not be entirely related to the sleep architecture alteration. A decreased motor cortex excitability probably exists in OSAS patients [42,44–48,88], whereas cortical MT is clearly not impaired in most of studies on RLS [49,50,52,54–60]. Therefore, a global pattern of hypoexcitability of the cortical–spinal neurons or the excitatory or inhibitory interneurons that project into these neurons might be a distinctive feature of OSAS patients only. Given that rMT is a global measure of cortical–spinal excitability and is believed to depend on glutamatergic synaptic excitability [23], it can be hypothesized that a dysfunction of the glutamatergic pathways exists in OSAS. Moreover, a recent study on an animal model of obstructive sleep apnea seems to confirm this finding showing that chronic intermittent hypoxia reduces the amplitude of both NMDA and non-NMDA glutamatergic excitatory currents evoked by stimulation of the second-order neurons in the nucleus tractus solitarii [89].

However, cortical excitability may be influenced also by the level of vigilance [65], thus it is unknown whether the different groups of patients had comparable levels of sleepiness and how this could influence the MT recording during the TMS sessions. EEG revealed the existence of a frontal thalamo-cortical dysfunction during sleep in OSAS patients [90], slowing in frontal and central cortical regions [78] and persistent brain dysfunction during wakefulness [91] that might explain these results.

Nevertheless, it is possible to hypothesize that hypoexcitability may be the result of a prevailing inhibitory GABAergic mechanisms, a finding which is clearly evident in patients with OSAS and not in those with RLS. In fact, a number of TMS studies indicates how the sleep disorders here considered differ in term of intracortical inhibitory phenomena. Notably, a significant prolongation of CSP has been described in OSAS [40,41,44,46], whereas the opposite has been reported in many studies on RLS [50,51,54,56,57,59]. OSAS and RLS also differ in intracortical excitability curves explored by means of the paired-pulse TMS paradigm. ICI is markedly reduced [49,52–55,59,60] whereas facilitation is normal or increased in RLS [49,52,55,60]. Conversely, paired-pulse curves of patients with OSAS and chronic insomnia are reported to be basically similar to controls [44,45,63,88].

The interpretation of these results becomes more difficult when we consider TMS research investigating cortex excitability changes after SD in healthy controls. These studies have produced conflicting results probably because of their small sample sizes and the different methodological approaches employed. Overall, however, the results seem to indicate that SD in healthy humans modifies the balance between inhibitory and excitatory cortical mechanisms and induces an “activating” pattern [64,66,70,71].

Finally, studies exploring the sensory-motor integration and the synaptic plasticity are very few and not homogeneous; therefore, it is not possible to compare reliably the TMS parameters of plasticity reported in the different clinical conditions considered here. Interestingly, in OSAS patients the pattern of TMS response from the genioglossus and the diaphragm muscles to facilitatory maneuvers differs from that of controls, indicating that the coupling between these two muscles during respiratory maneuvers (previously reported in normal subjects [43]) is particularly evident in OSAS patients, probably being a response to plastic adaptive changes occurring at the level of the brainstem motoneurons or their cortical representation [42]. Moreover, as stated, OSAS has a disease severity-correlated increase of central motor conductivity to the genioglossus that might be the expression of a facilitation or a central compensatory mechanism [43]. Nevertheless, recent evidence showed that plasticity-related process might be impaired in OSAS patients since both rTMS and TBS were unable to modify TMS measures of cortical excitability, suggesting a widespread alteration in cortical neurophysiology of OSAS patients too [46].

Event-related potentials have revealed that changes in cognitive attentive processing, a common trait in patients with OSAS, might

reflect impaired functioning of the prefrontal cortex and an involvement of cortical associative areas [92]. However, structural and functional MRI in patients with OSAS has shown a reduction of gray matter density in different brain areas or an impairment of activation during different tasks, considered as an adaptive compensatory mechanism [93]. A different mechanism of neuronal reorganization might be present in patients with RLS. It is known that RLS is characterized by uncomfortable sensations in the legs coupled with an irresistible urge to move them. Different studies have suggested that this disorder is related to abnormalities in inhibitory pathways occurring at the level of the integration of sensory-motor input, as confirmed by the study on SAI by Rizzo et al. [60]. According to these findings, TMS parameters mainly mediated by GABAergic transmission, such as CSP and SICI, were found to be reduced in RLS, thus supporting the impairment of inhibitory pathways in RLS. Moreover, neurophysiological studies in RLS patients showed wake EEG abnormalities [94], highlighting that cognitive dysfunction in RLS may be related to cortical involvement [79], whereas other studies have demonstrated alteration of the synaptic plasticity [53,54,59,60]. Taken together, data on RLS seem to indicate that a dysfunction in the process of motor skill learning, such as a reduction or an alteration in movement-related cortical plasticity, might be hypothesized [54,59].

In conclusion, the data we have reviewed seem to indicate that the third scenario that we have devised at the beginning of this study is the most probable one. The global results of the TMS studies indicate that each of the sleep disorders considered here is characterized by a set of abnormal and normal parameters. Although there is no specific single measure able to distinguish the conditions between each other the set of abnormal parameters of each clinical condition seem to represent a somewhat disease-specific pattern, probably connected with their different neurobiological bases. This has nontrivial consequences for the use of this techniques in the understanding of these sleep disorders and for the eventual evaluation of the effect of therapy. Although TMS and its related techniques do not provide specific hallmarks of disease, they allow to explore non-invasively and *in vivo* the global weight of several neurotransmitters, providing further insights on the pathophysiological and neurochemical basis underlying sleep disorders.

Practice points

1) Transcranial magnetic stimulation is a widely used, non-invasive neurophysiological technique capable to assess, painlessly and safely, cortical excitability in different sleep disorders.
2) The methodological approach used (and especially the level of vigilance) needs to be taken into account when considering the results from transcranial magnetic stimulation studies in sleep disorders.
3) Findings seem to converge on a global profile of cortical hypoexcitability in obstructive sleep apnea syndrome, in an impairment of intracortical inhibitory pathways in restless legs syndrome and in an intracortical inhibitory/excitatory imbalance in insomnia and in sleep deprivation. Cortical plasticity phenomena are involved.
4) Changes of transcranial magnetic stimulation measures of motor cortex excitability described in obstructive sleep apnea syndrome, restless legs syndrome, insomnia and in sleep deprivation might be somewhat disease-specific rather than a general consequence of non-specific sleep loss and instability.

Research agenda

1) A fully powered study, using the same stimulation and recording procedures and measuring the same complete set of parameters is needed to compare directly obstructive sleep apnea syndrome, restless legs syndrome and insomnia, and to confirm the conclusions of this review.
2) Sleep and neurochemistry: exploring neurotransmission pathways sheds light on the neurochemical basis underlying sleep disorders and helps to identify novel targets for therapeutic interventions.
3) Sleep and neuroimaging: the eventual correlation between transcranial magnetic stimulation data and functional and brain connectivity imaging needs to be explored.
4) Transcranial magnetic stimulation in the diagnostic process and treatment of sleep disorders: transcranial magnetic stimulation as an added value in the assessment of sleep disorders, evaluation of the effect of therapy, and design of non-pharmacological approaches (such as repetitive transcranial magnetic stimulation and theta burst stimulation).

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